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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/051,231	01/22/2002	Staffan Nilsson	000510-007	7956
7590	12/09/2004		EXAMINER	
Ronald L. Grudziecki BURNS, DOANE, SWECKER & MATHIS, L.L.P. P.O. Box 1404 Alexandria, VA 22313-1404			DEJONG, ERIC S	
			ART UNIT	PAPER NUMBER
			1631	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/051,231	NILSSON ET AL.	
	Examiner	Art Unit	
	Eric S. DeJong	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 27 September 2004.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-46 is/are pending in the application.
- 4a) Of the above claim(s) 1-20,23-28,38, and 41 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 21,22,29-37,39,40 and 42-46 is/are rejected.
- 7) Claim(s) 22 and 35 is/are objected to.
- 8) Claim(s) 1-46 are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 2 pages.
- 4) Interview Summary (PTO-413)
Paper No(s)/Mail Date: _____.
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: _____.

DETAILED ACTION

The communication by applicant filed on 27 September, 2004 containing an amendment to the specification and an amended list of claims is noted. The change in title of the instant application is accepted as "Method for Screening Crystallization or Amorphous Stage Conditions for Molecules". The amended list of claims 1-46 is accepted and replaces all previous claims for the instant application. It is acknowledged that these amendments to the application do not constitute new matter.

Election/Restrictions

Applicant's election with traverse of Group III (claims 21, 22, and 29-34), election of multi-angle light scattering in combination with Raman spectroscopy as the specie of detection practice, election of acoustic levitating as the specie of levitating practice, and election of a substance influencing nucleation conditions as the specie of substance delivered to the levitated droplet in the reply filed on 27 September, 2004 is acknowledged.

The traversal is on the ground(s) that it would not be an undue burden upon the Examiner to examine all three groups of claims at the present time. This is not found persuasive as applicants do not argue or specifically negate the distinctness between the groups and species that were set forth in the previous office action, mailed on 25 June, 2004.

The distinction between Group II and Groups I and III was demonstrated as the product as claimed can be used in a materially different process of using that product

(MPEP § 806.05(h)). In the instant case the system of Group II can be used in materially the different process of producing phase changes that occur via nucleation events such as gas condensation into a liquid as in Group I or crystallization of a molecule as in Group III. The materials detected via nucleation of Groups I and III are also distinct usages of the system of Group II each being directed toward nucleation related to fluids and gases vs. crystallization process.

Separate species of detection practices as set forth in claims 2, 3, 15, or 16 are distinct and separately published and described in literature thus demonstrating an undue burden if searched together. Separate species of levitating practices as set forth in claims 4 or 13 are distinct and separately published in literature thus demonstrating an undue burden if searched together. Species of substance delivered to the levitated droplet as set forth in claims 6, 18, 24, 25, 27-34, or a non-specified generic substance (as set forth in claims 7 or 19) are distinct and separately published in literature thus demonstrating undue burden if searched together.

Thus applicants' traversal argument was not directed to the basis of the restriction and specie elections. Therefore the restriction and specie election requirements are held as proper and therefore made FINAL.

Claims 1-20 and 23-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in the reply filed on 27 September, 2004.

Claims 38 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected specie, there being no allowable generic or linking claim. Claim 38 does not read on the elected specie of detection practices as it is drawn to detection by visual surveillance. Applicant timely traversed the election requirement in the reply filed on 27 September, 2004.

Claim 41 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected specie, there being no allowable generic or linking claim. Claim 41 does not read on the elected specie of substance delivered to the levitated droplet as it is drawn to a substance that is a protein, a membrane protein, a peptide, an enzyme, a receptor, a drug compound, nucleic acid, a macromolecule, a macromolecular assembly, or complexes thereof. Applicant timely traversed the election requirement in the reply filed on 27 September, 2004.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Objections

The disclosure is objected to because of the following informalities:

Claims 22 and 35 contain improper periods in the parts therein. Each claim is to begin with a capital letter and end with a period. Periods may not be used

elsewhere in the claims except for abbreviations. See MPEP § 608.01 (m). Appropriate corrections are required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21, 22, 29-36, 39, 40, and 42-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arnowitz et al. taken in view of Danley et al. and Schwartz et al.

Claims 21, 35, 36, 39, and 42 are drawn to a system for screening crystallization or amorphous stage conditions of a molecule comprising at least one acoustic levitator for positioning at least one droplet, at least one dispenser for delivering at least one substance that influences nucleation conditions to the positioned droplet, and one or more means of detecting nucleation tendency in the at least one droplet by means of multiple-light scatter in combination with Raman spectroscopy.

Arnowitz et al. teaches an apparatus for controlling dynamic, reagent induced transformations of multiple biological samples being crystallized (screening crystallization or amorphous stage conditions of a molecule). See Arnowitz et al., paragraphs 0001 and 0014. The disclosed invention allows for the positioning of one or more samples in separate crystallization chambers (at least one droplet). See Arnowitz et al., paragraphs 0088 and 0090. The disclosed invention supports a delivery system by which multiple reagents effecting nucleation conditions can be delivered to samples within the crystallization chambers (at least one dispenser for delivering at least one substance that effects nucleation). See Arnowitz et al., paragraph 0072, 0078, and 0082. The disclosed invention supports multiple optical sensors that detect one or more features of light that has traveled through a sample providing measurements of light

absorption, occlusion, refraction or scattering (one or more means of detecting nucleation conditions).

Arnowitz et al. does not teach the use of at least one levitator for positioning at least one droplet, but rather relies upon separate chambers to accommodate small sample quantities of the molecule to be crystallized in recognition of the desirability to meet demands of sample cost and availability. See Arnowitz et al., paragraph 0095. Further, Arnowitz et al. teaches that sample conditions that effect nucleation (the desired state of the state of the sample), such as temperature, protein concentration, salt solution concentration, pH and gravitational field, must be carefully and precisely controlled during experimentation to obtain optimum crystal growing conditions (Arnowitz et al., paragraph 0004).

Danley et al. teaches the use of acoustic levitation with an acoustic levitation device wherein the force of sound waves are used to suspend, position or manipulate an object such as a solid or liquid (levitating a fluid droplet using an acoustic levitation device). Danley et al., column 1, second full paragraph specifically sites that "...potential applications [of an acoustic levitator] exist when ever there is need to hold, move, store, position, or process an object without contact to any surface, particularly if such contact would damage or contaminate the object or otherwise interfere with some desired property or state."

Arnowitz et al. teaches the use of multiple optical sensors that detects one or more features of light that has traveled through a sample, such as scattered light, but

does not specifically teach Raman spectroscopy as a suitable means of nucleation detection.

Schwartz et al. teaches the specific use of Raman spectroscopy for monitoring protein concentration to report on nucleation conditions of a sample being crystallized. See Schwartz et al., Abstract. Further, Schwartz et al. asserts that Raman spectroscopy is ideal for biochemical experiments in aqueous media (see Schwartz et al., Introduction, final paragraph) and that the disclosed application of the technique greatly enhances the process of determining the necessary criteria for protein crystal growth.

Thus, it would be obvious to one skilled in the art to use one or more acoustic levitation devices with a system for screening crystallization conditions so as to levitate at least one droplet, administer at least one substance affecting nucleation conditions, and detect nucleation by means of multiple-light scattering in combination Raman spectroscopy in order to satisfy and maintain the stringent conditions required for protein crystallization as disclosed by Arnowitz et al. and taken in view of Danley et al. and Schwartz et al.

Claim 22 is drawn to a system for screening crystallization or amorphous stage conditions of a molecule comprising at least one acoustic levitator for positioning at least one droplet, at least one dispenser for delivering at least one substance that influences nucleation conditions to the positioned droplet, one or more means of detecting nucleation tendency in the at least one droplet by means of multiple-light scatter in combination with Raman spectroscopy, and scoring nucleation tendency.

In addition to that presented above, Arnowitz et al. teaches that multiple optical sensors are used to examine the physical or chemical state of a sample in a crystallization cell, determine the changes in the sample state, and then from an analysis of that determination either repeat earlier steps of adding reagents to samples to optimize crystallization conditions or repeat a set of conditions that produced crystals. See Arnowitz et al., paragraphs 0022, 0024, 0028, and 0034. A reasonably broad interpretation of scoring nucleation tendency is an evaluation of a given set sample conditions so as to provide a basis to make rational changes that may lead to optimized set of conditions that lead to crystal formation.

Thus, it would be obvious to one skilled in the art to use one or more acoustic levitation devices with a system for screening crystallization conditions so as to levitate at least one droplet, administer at least one substance affecting nucleation conditions, detect nucleation by means of multiple-light scattering in combination Raman spectroscopy, and score nucleation tendency in order to satisfy and maintain the stringent conditions required for protein crystallization as disclosed by Arnowitz et al. taken in view of Danley et al. and Schwartz et al.

Claim 32 is drawn to a system for screening crystallization or amorphous stage conditions of a molecule comprising at least one acoustic levitator for positioning at least one droplet, at least one dispenser for delivering at least one substance that influences nucleation conditions to the positioned droplet, one or more means of detecting nucleation tendency in the at least one droplet by means of multiple-light

scatter in combination with Raman spectroscopy, and scoring nucleation tendency, wherein the molecule is a protein, a peptide, a membrane protein, a peptide, an enzyme, a receptor, a drug compound, **OR** a nucleic acid. Claim 33 further requires that said peptide be an oligopeptide or a polypeptide. Claims 34 further requires that said nucleic acid be DNA, RNA, an oligonucleotide, or a polynucleotide

In addition to that presented above, Arnowitz et al. teaches that suitable samples for use in the invention are small and large molecules which include, but not limited to, macromolecules, proteins, nucleic acids, ligands and drugs (comprising a drug compound). See Arnowitz et al., paragraph 0017.

Thus, it would be obvious to one skilled in the art to use one or more acoustic levitation devices with a system for screening crystallization conditions so as to levitate at least one droplet, administer at least one substance affecting nucleation conditions, and detect nucleation by means of multiple-light scattering in combination Raman spectroscopy, and scoring nucleation tendency in order to satisfy and maintain the stringent conditions required for protein crystallization as disclosed by Arnowitz et al. taken in view of Danley et al. and Schwartz et al, wherein the molecule is a protein, a peptide, an oligopeptide, a polypeptide, a membrane protein, a peptide, an enzyme, a receptor, a drug compound, a nucleic acid, DNA, RNA, an oligonucleotide, **OR** a polynucleotide.

Claim 40 is drawn to a system for screening crystallization or amorphous stage conditions of a molecule comprising at least one acoustic levitator for positioning at

least one droplet, at least one dispenser for delivering at least one substance that influences nucleation conditions to the positioned droplet, and one or more means of detecting nucleation tendency in the at least one droplet by means of multiple-light scatter in combination with Raman spectroscopy, wherein the at least one sample droplet is in the range of 1 fL to 100 μ L.

In addition to that presented above, Arnowitz et al. teaches that small sample quantities are desirable to meet demands of sample cost and availability. See Arnowitz et al., paragraph 0095. While no sample volume range is not specifically indicated, it is clearly asserted that the best mode of operation for any embodiment of the invention will employ the smallest possible amount of sample.

In addition to that presented above, Danley et al. disclose that the interference patterns of the generated sound waves produce standing nodes where a sample will be held fixed. Danley et al. does not disclose specific ranges of droplet volumes for levitation. The issue of sample volume is however addressed in the discussion of standing nodes, or energy wells, that provide the resultant force which keeps a sample droplet in fixed space. See Danley et al, Column 3, lines 27-44. There is no theoretical lower limit to the size of a droplet that may be fixed in the standing node, however the upper limit size of the droplet can reasonably be estimated as half of the wavelength of the sound generated by the levitator. A sample droplet size at or below 100 μ L in volume, having a radius equal to or less than 4 mm, can be accommodated by an acoustic levitator as disclosed by Danley et al. An embodiment of this is provided in Ishikawa et al. operating at a 20 kHz frequency with a corresponding wavelength of 15

mm. Ishikawa et al. demonstrated the stable levitation of 4 mm radius liquid droplet, corresponding to a 100 μL volume, for more than 200 hours. See Ishikawa et al., 2.3 Levitation of a liquid droplet, first full paragraph.

Thus, it would be obvious to one skilled in the art to use one or more acoustic levitation devices with a system for screening crystallization conditions so as to levitate at least one droplet within the range of 1 fl to 100 μL , administer at least one substance affecting nucleation conditions, and detect nucleation by means of multiple-light scattering in combination Raman spectroscopy in order to satisfy and maintain the stringent conditions required for protein crystallization as disclosed by Arnowitz et al. taken in view of Danley et al. and Schwartz et al.

Claim 43 is drawn to a system for screening crystallization or amorphous stage conditions of a molecule comprising at least one acoustic levitator for positioning at least one droplet, at least one dispenser for delivering at least one substance that influences nucleation conditions to the positioned droplet, and one or more means of detecting nucleation tendency in the at least one droplet by means of multiple-light scatter in combination with Raman spectroscopy, wherein the illumination source is arranged so that the at least one levitated droplet is positioned around the illumination source in a way that each suspended droplet can be illuminated by rotating light..

In addition to that presented above, Arnowitz et al. teaches controlling the position of the sensor which detects changes in sample conditions, said sensor comprising elements for both an illumination source and a detection means. Controlling

the position of the sensor necessarily implies the capability of moving the sensor relative to the sample position. Thus it is within the scope of the Arnowitz et al. teachings to move the illumination source relative to a sample and impart rotating light. Additionally, an embodiment of the invention provided in Figure 3 and described in the corresponding paragraph 003 employs a carousel to rotate different samples beneath a fixed optical sensor. In a coordinate system where the origin is placed at the sample's position and considered fixed, the illumination source would be viewed as rotating light relative to the sample.

Thus, it would be obvious to one skilled in the art to use one or more acoustic levitation devices with a system for screening crystallization conditions so as to levitate at least one droplet, administer at least one substance affecting nucleation conditions, and detect nucleation by means of multiple-light scattering in combination Raman spectroscopy, wherein the illumination source is arranged so that the at least one levitated droplet is positioned around the illumination source in such a way that each suspended droplet can be illuminated by rotating light. in order to satisfy and maintain the stringent conditions required for protein crystallization as disclosed by Arnowitz et al. taken in view of Danley et al. and Schwartz et al.

Claims 21, 35, 36, 37, 39, and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arnowitz et al. taken in view of Danley et al., Schober et al., and Schwartz et al.

Claim 37 is drawn to a system for screening crystallization or amorphous stage conditions of a molecule comprising at least one acoustic levitator for positioning at least one droplet, at least one dispenser for delivering at least one substance that influences nucleation conditions to the positioned droplet, and one or more means of detecting nucleation tendency in the at least one droplet by means of multiple-light scatter in combination with Raman spectroscopy, wherein the dispenser is a piezoelectric dispenser.

As presented above, Arnowitz et al. teaches a delivery system by which multiple reagents that effect nucleation can be delivered to samples, but does not teach the specific use of a piezoelectric dispenser for delivering a substance that effects nucleation.

Schober et al. taken as a whole teaches using a piezoelectric dispenser for the accurate microdispensation of biochemically relevant solutions and suspensions. Further, Schober et al. teaches that manual and mechanical means of dispensing liquids are insufficient for accurate sample dispensation of very small volumes, but the disclosed piezoelectric transducer device provides dispensation of very small volumes without any detectable impact on the biological function of dissolved or suspended molecules. See especially Schober et al., abstract.

Arnowitz et al. teaches that small sample quantities are desirable to meet demands of sample cost and availability (See Arnowitz et al., paragraph 0095) and that sample conditions must be carefully and precisely controlled during experimentation to obtain optimum crystal growing conditions (Arnowitz et al., paragraph 0004).

In view of Schober et al., it would be obvious to one skilled in the art to use a piezoelectric dispenser to deliver one or more substances that effect nucleation to a suspended sample droplet in a system as disclosed by Arnowitz et al. taken in view of Danley et al. and Swartz et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on Monday-Friday during the hours of 8:30AM-5:00PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

EDJ



Ardin H. Marschel 12/6/04
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PRIMARY EXAMINER